

In the longer term, however, midwives have to face a more important question. Do they want their profession to be regulated by disciplinary procedures designed primarily for nurses? Midwives are practitioners in their own right. Doctors are not governed by firm rules, and the General Medical Council recognises the importance of individual judgment in clinical matters. Though the midwives' rules should remain, at least for the time being, the midwives' disciplinary system should be seen to recognise how delicate the interpretation of these rules may be. The high court, which hears appeals against UKCC decisions, should not be the forum in which midwives regulate themselves. A separate disciplinary system

for midwives that recognises their status as practitioners may be the best way to avoid further damaging public disputes.

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## Regular Review

# Recent research on the causes of Alzheimer's disease

## *What causes neuronal death, and why the specific patterns?*

Alzheimer's disease is now the commonest primary degenerative dementia, accounting for at least half of all the cases of dementia examined at necropsy. As the numbers of elderly people in our population increase, moreover, it will become one of the most frequent causes of death, affecting at least a 20th of those aged over 65 and as many as a quarter over 80. Until 20 years ago Alzheimer's disease was regarded as one of the inevitable consequences of aging, but recent research has shown that this is too simple a picture.

The neuropathological changes in Alzheimer's disease are characteristic: neuronal loss, senile plaques, and neurofibrillary tangles. So it was natural to conclude that here was a disease entity, with its own causes, natural course, and potential specific treatment. Such a conclusion gained impetus from the discovery of the cholinergic deficit in Alzheimer's disease. Central cholinergic systems had already been implicated in neuropharmacological models of memory and so it seemed plausible that the profound memory disturbances in Alzheimer's disease were caused by a selective loss of cholinergic neurones.<sup>1</sup> Soon it became clear, however, that the picture was by no means so simple. Deficits were consistently found in other brain neuropeptides, particularly corticotrophin releasing factor<sup>2</sup> and somatostatin.<sup>3</sup>

The clinical features (memory deficits, poor judgment, and deterioration in temperament and behaviour) lead gradually and indirectly to death and so impair the demented patients that they need full time care. These same clinical features point to a large problem for research. We know so little about the biological basis of higher mental functions that we cannot distinguish which among the many known abnormalities produce the symptoms and which initiate the disease. Here we review the recent studies on molecular mechanisms in the causes of Alzheimer's disease.

### Genetic studies

Although only one in 1000 of the general population under the age of 65 has Alzheimer's disease,<sup>4</sup> about one in three patients with the condition have a similarly affected first degree relative—a pattern consistent with the effects of an autosomal dominant gene.<sup>5</sup> Nevertheless, such a finding does not necessarily imply a genetic cause: shared environmental factors might be responsible and in any case the incidence might be exaggerated by selective reporting.

Studies of twins can help evaluate the genetic and environmental factors. Kallman *et al* studied 108 pairs of twins in whom each index twin had senile dementia (in most cases diseases like Alzheimer's), finding that monozygotic twins had a rate of concordance of 43%, dizygotic twins 81%, siblings 7%, and parents 3%.<sup>6</sup> Hence, though genetic factors are an important causal factor, others also play an appreciable part—a point emphasised in other studies.<sup>7</sup>

Another genetic angle has come from neuropathological studies of middle aged patients dying with Down's syndrome who show changes indistinguishable from Alzheimer's disease.<sup>8</sup> The inference often drawn is that excess genetic material on chromosome 21 may cause Alzheimer's disease. This has stimulated much research for a specific gene on chromosome 21 coding for a protein associated with abnormal aging or neuronal death, in which cerebral amyloidogenic proteins have provided a starting point. Intracellular amyloid consists mostly of neurofibrillary tangles made up of paired helical filaments. Extracellular amyloid is the main protein component of amyloid filaments deposited as plaques among degenerating neurones near the cerebral vessels.<sup>9,10</sup> Vascular amyloid is now known to be part of a much larger precursor, possibly a membrane structure, with its gene on chromosome 21.<sup>11</sup> Early in 1987 the pedigrees of four families were described in which Alzheimer's disease seemed to be an autosomal dominant, the genetic defect also being on chromosome 21.<sup>12</sup> Soon it was being suggested that the "familial Alzheimer gene" and the amyloid protein gene were identical.<sup>13</sup> Further studies showed, however, that these claims could not be supported: in familial Alzheimer's disease the disorder does not segregate exclusively with the amyloid protein gene and this gene is not present in excess in either sporadic Alzheimer's disease or Down's syndrome.<sup>14,15</sup> It is now clear that the gene for the amyloid protein is not the gene for familial Alzheimer's disease and is not the cause of Alzheimer's disease.<sup>16</sup> Nevertheless, abnormalities in the control of the synthesis of cerebral amyloidogenic proteins may still be shown to contribute to Alzheimer's disease.

More immediately relevant is the application of these genetic observations to the threshold model of Alzheimer's disease.<sup>17</sup> In the familial condition the genetic contribution would be less than in Down's syndrome and the contribution of factors related to age would be greater. In so called

"sporadic" cases the contribution of aging would be more important than genetic factors.<sup>18</sup>

In Down's syndrome, Alzheimer's disease, and several genetically determined conditions with chronic neurological sequelae there is an impaired ability to repair DNA damage induced by a wide range of agents,<sup>19</sup> and the neurones might be particularly affected. A further topic for research has concerned nerve growth factor, a protein present at the terminals of cholinergic neurones in the basal nuclei that affects their function.<sup>20</sup> Rats with experimentally induced lesions resembling those in Alzheimer's disease had the degenerative process alleviated after treatment with nerve growth factor. Intraventricular injections of nerve growth factor improved the performance of aged rats in a spatial memory task.<sup>21</sup> Hence a defect in the synthesis or action of nerve growth factor might contribute to the loss of neurones concerned with memory that occurs in Alzheimer's disease.

These and other lines of evidence suggest that there are potentially multiple defects in Down's syndrome leading to the neuropathological changes in Alzheimer's disease: (a) an accumulation of a toxic metabolic product of an enzyme coded on chromosome 21; (b) synthesis of excess receptors that exaggerate the effects of a neurotoxin; (c) severely restricted adaptive capacity, related to malformation of the brain<sup>22</sup>; (d) impaired capacity to repair damage to DNA caused by an endotoxin; and (e) absence of a neurotrophic factor.<sup>23</sup>

### Infective agents

Studies on scrapie, a neurodegenerative disease of sheep, provided the first clue for a role for infection in Alzheimer's disease. Unlike other infective agents, scrapie causes no fever or inflammatory or immune responses. When inoculated into mice scrapie produces neuropathological changes that include neuritic plaques and a reduced activity of cholinergic synthetic enzymes.<sup>24</sup> Scrapie may be caused by an infectious pathogen known as a prion, a protein without detectable nucleic acids. An original proposal was that the similar staining reactions of aggregates of prions and plaques indicated that they might be identical.<sup>25</sup> Later studies suggested, however, that the amyloid proteins of both the blood vessels and the plaques are distinct from that of prions.<sup>26</sup> But do prions cause scrapie or are they part of the cellular response derived by the host to another, unknown, causal agent?

A gene coding for prion protein has now been located in the human genome on chromosome 20,<sup>27,28</sup> not, as predicted by the Down's model of Alzheimer's disease, on chromosome 21. Possibly this protein might be concerned in the pathogenesis of Alzheimer's disease, arising either from a process initiated by a pathogen or as part of the pathogen itself. Against this theory, however, is the failure to transmit Alzheimer's disease to animals, which is strong evidence against the role of an infectious agent.<sup>29</sup>

### Metabolism and toxins

Much evidence points to a defect in intraneuronal transport in Alzheimer's disease. Proteins associated with the microtubules forming the framework of the neurones can be detected in the characteristic tangles,<sup>30</sup> and one of the proteins (tau) may be an important constituent of the paired helical filament.<sup>31,32</sup> Moreover, assembly of microtubules is disrupted in Alzheimer's disease. A critical concentration of tubulin is necessary for this process, and its concentration is low in postmortem specimens of temporal cortex taken from patients with Alzheimer's disease.<sup>33</sup> Preparations from normal brains taken two to four hours after death can form microtubules whereas those from patients with Alzheimer's disease

cannot, although both can form neurofilaments.<sup>34</sup> Moreover, specimens from the diseased brains have no abnormality in tubulin and no microtubule inhibitor and their tau protein is abnormally phosphorylated. When DEAE dextran (which mimics the effect of tau protein) was added it induced the formation of microtubules. Finally, preliminary reports indicate that protein A68, a phosphokinase for tau protein, is greatly increased or exclusively present in the brain and the spinal fluid of patients with Alzheimer's disease.<sup>35</sup> Thus abnormal phosphorylation of tau protein may be a key step in the formation of neurofibrillary tangles, although the origin of the abnormality remains obscure.

Tau protein antigens have been shown in the intracellular inclusions of Pick's disease and progressive supranuclear palsy, which suggests that a tau protein abnormality may be found in other conditions<sup>36</sup> and that the abnormality may be only one of several factors that lead to cellular disruption.

Apart from mechanical disruption and cytoskeletal abnormalities, the neurones of patients with Alzheimer's disease might be vulnerable to peroxidation by free radicals. Damaging free radicals are metabolised within the cells by the enzyme superoxide dismutase. The enzyme produces peroxide, an oxidant, which is rendered harmless in the brain by the enzyme glutathione peroxidase. The gene for superoxide dismutase is located on chromosome 21, and in trisomy 21 (Down's syndrome) its activity is increased by a half, leading to an excess of peroxide. In patients with Down's syndrome there is a significant correlation between intelligence and glutathione peroxidase activities.<sup>37</sup> In patients with Alzheimer's disease the activity of the superoxide dismutase in the brain is no different from that in controls, whereas the activity of glutathione peroxidase is raised, which suggests that the neurones may suffer increased oxidative damage.<sup>38,39</sup> The increased activities of glucose 6-phosphate dehydrogenase and glucose 6-phosphogluconate dehydrogenase that are found in Alzheimer's disease may be due to increased metabolism of brain peroxide.<sup>40</sup>

The successful disposal of free radicals results in membranes retaining their fluidity and a reduced accumulation of intracellular pigment. Oxidative damage can be measured by decreased fluidity of platelet membranes and occurs in normal aging as well as in patients with Down's syndrome.<sup>41</sup> Contrary to expectations, however, in patients with Alzheimer's disease the fluidity of platelet membranes is increased, and this may correlate with the severity of the dementia.<sup>42</sup> Hence Alzheimer's disease does not just represent accelerated aging and the cause of increased fluidity of membranes is not known.

Processing of information is carried out most effectively by neurones that have efficient oxidative processes. These processes are depressed both by aging and by Alzheimer's disease.<sup>43</sup> With positron emission tomography a high correlation can be shown between intelligence scores and the rate of metabolism of glucose in both patients with Alzheimer's disease and normal controls<sup>44</sup>; in the patients, however, cerebral metabolism of glucose is both decreased and different between the right and left cerebral hemispheres.<sup>45</sup>

### Does a toxic or deficiency state lead to Alzheimer's disease?

Aluminium, the most abundant metal on the earth's crust, is an important toxic agent in dialysis dementia, though this differs clinically from the dementia in Alzheimer's disease. Neurofibrillary tangles composed of 10 nm filaments can be induced in animals by the intracerebral injection of aluminium salts,<sup>46</sup> but these are different from the tangles in Alzheimer's disease.<sup>47,48</sup> Reports of the accumulation of alu-

minium in the brains of patients with Alzheimer's disease<sup>49 50</sup> have not always been confirmed.<sup>51</sup>

Possibly, however, aluminium may play an indirect part by altering the metabolism of minerals. Three geographically distinct populations show a considerable increase in the incidence of a neurodegenerative complex: the Chamorros of the island of Guam in the Marian islands; the Auyu and the Jolu people of western New Guinea; and the Japanese of the Hobara and Kozagarra districts of the Kii peninsula of Honshu island. Neuropathologically the patients have the features of motor neurone disease, Parkinson's disease, or Alzheimer's disease, or combinations of these. It has been postulated that the incidence of this complex of diseases varies with local geology<sup>52</sup>; Guam, the Kii peninsula, and western New Guinea share low concentrations of calcium and magnesium in the soil and drinking water and high concentrations of aluminium and iron.<sup>53</sup>

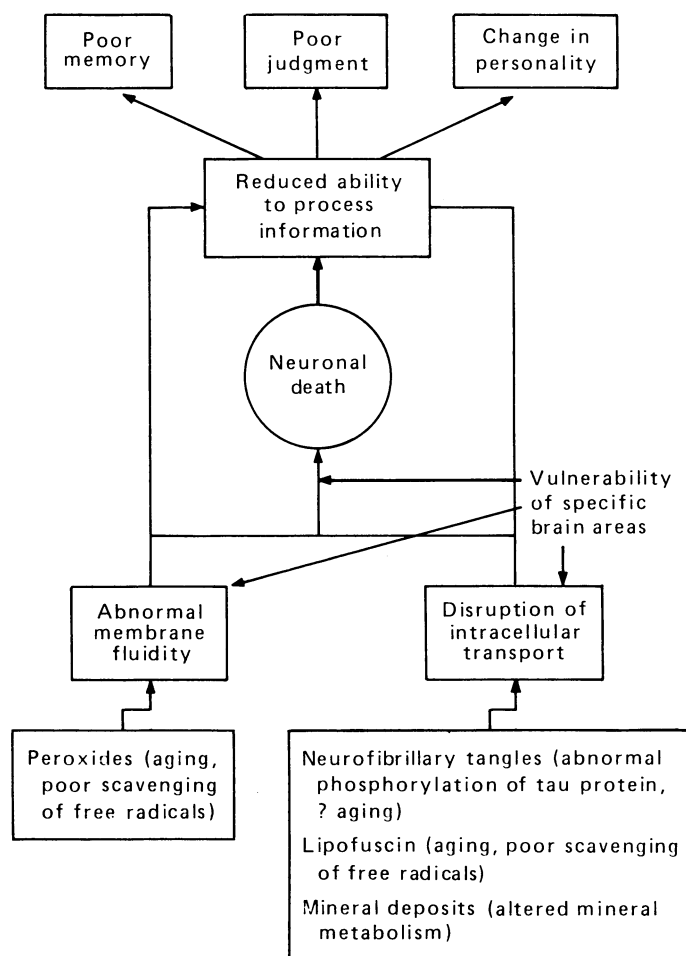
Clinical studies of patients of the Chamorros people have shown abnormalities in the metabolism of calcium and vitamin D and their brains at necropsy have shown intra-neuronal deposition of both calcium and aluminium.<sup>54 55</sup> A recent review has concluded that there is considerable support for the hypothesis of a defect in mineral metabolism in these neurodegenerative disorders,<sup>56</sup> which have declined with the introduction of calcium and magnesium to the areas. The areas have also become increasingly Westernised and the local diet has moved away from dependence on flour made from the cyad nut. This and other evidence has led to recent suggestions of an alternative hypothesis: a nutritional change has reduced the incidence of the disorders, which may have been caused by "free excitatory" neurotoxic amino acids such as  $\beta$ -N-methylamino-L-alanine.<sup>57 58</sup> Migrants from these areas have developed the disorders years later, suggesting that an environmental insult interacts with the aging process leading to the disorder once a threshold has been passed.

If environmental causes are responsible for the complex of parkinsonism-dementia of Guam then they may contribute to the similar neurofibrillary tangles of Alzheimer's disease. Aluminium and silicon are found in the cores of senile plaques,<sup>59</sup> and x ray microanalysis has shown calcium and aluminium together in the affected neurones from patients with parkinsonism-dementia of Guam.<sup>60</sup> This deposition may lead to impaired axonal transport and facilitate the formation of neurofibrillary tangles. But is this indeed the sequence of events? Aluminium and silicon deposition might follow the abnormal accumulation of cytoskeletal elements found in the neurofibrillary tangles and plaques.<sup>61</sup> Dystrophic mineralisation such as that found in Alzheimer's disease and the parkinsonism-dementia of Guam may also follow abnormal calcium metabolism, and there is some evidence for disordered calcium metabolism in Alzheimer's disease. Calcium homeostasis is altered by aging but more so by Alzheimer's disease.<sup>43</sup> Increased concentrations of bound cell calcium are found in the skin fibroblasts in Alzheimer's disease when patients are compared with controls. Other alterations in calcium metabolism in the nervous system suggest that these may have a role in Alzheimer's disease.<sup>62-65</sup>

## Conclusions

All the evidence we have discussed does not provide temporal sequence of the pathogenesis of Alzheimer's disease. In broad terms, however, there are two possibilities. Firstly, Alzheimer's disease may be a single disease process with a fixed sequence of pathological changes. Each of the abnormalities described above would then represent a necessary link in such a causal chain, leading to the death of specific

populations of cells. Secondly, like motor neurone disease, Alzheimer's disease may be the end point of many distinct pathways, each of which can lead to neuronal death. Some patients will develop Alzheimer's disease in a manner akin to Down's syndrome so that genes from chromosome 21 are sufficient to produce all the neuropathological changes and clinical features. Other patients may cross a threshold for the disease only after an initiating event such as a head injury<sup>66</sup> or exposure to a neurotoxin.<sup>67</sup>



*Some suggested relations among possible causal factors (given in parentheses) in Alzheimer's disease, the selective loss of neurones, and the principal symptoms of the disorder*

Whatever the eventual answer, two main themes emerge from the results of research. Firstly, there is considerable support for the notion that neuronal integrity may be compromised in Alzheimer's disease by both intracellular disruption and abnormal fluidity of membranes. Secondly, there is little to indicate why there is a specific pattern of cell death, but the circumscribed distributions of certain proteins in the brain (for instance, calmodulin) are possible starting points for further research. Above all we must answer the two key questions (figure): Why do neurones die? And why do they die in specific patterns leading to characteristic clinical syndromes?

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